REMARKS

Reconsideration and withdrawal of any rejections of the application, and allowance of the claims, especially in view of the amendments and remarks made herein, and the enclosures herewith, are respectfully requested.

I. STATUS OF THE CLAIMS

Claims 47-72 are pending in the application. Claims 52 and 54 have been amended, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is respectfully submitted that the claims herewith and the claims as originally presented are and were in full compliance with the requirements of 35 U.S.C. §§101, 102, 103 and 112. The amendments to these claims, and remarks concerning these claims, were not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather for clarification and to round out the scope of protection to which the Applicant is entitled.

Support for the amended recitations is found throughout the specification and in the originally filed claims.

II. INFORMATION DISCLOSURE STATEMENT

The Examiner's attention is respectfully directed towards the document on the enclosed PTO form 1449. This Information Disclosure Statement is being filed after receipt of a final Office Action such that enclosed is the required fee of $180.00 set forth in §1.17(p) for consideration and entry of this document.

Pursuant to 37 CFR §1.97(d), Applicants petition the Commissioner to consider this Information Disclosure Statement, and to make of record the document cited on the accompanying PTO form 1449.

Pursuant to 37 CFR 1.97(e)(2), it is certified that no item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application; and, to the knowledge of the undersigned after making reasonable inquiry, such document was not known to any individual designated in 37 C.F.R. 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

This information disclosure is not a representation that the cited document is considered pertinent, or that the cited document is indeed prior art.

In view of the above, Applicants respectfully request that the petition be granted and that the Examiner consider the relevance of this document to the claims, and make the document of record in this application and that a copy of Form PTO-1449 be initialed by the Examiner and returned to the undersigned.

III. THE OBJECTIONS TO THE APPLICATION ARE OVERCOME

The November 21, 2003 Office Action requested correction of the title of the present application. The objection is respectfully traversed. Such amendment has been made herewith, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, rendering the objection moot. Consequently, reconsideration and withdrawal of the objection to the application is respectfully requested.

Additionally, the Office Action requested correction of the abstract so as to more accurately describe the claimed subject matter of the present application. The objection is respectfully traversed. Such amendment has been made herewith, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, rendering the objection moot. Consequently, reconsideration and withdrawal of the objection to the application is respectfully requested.

IV. THE OBJECTIONS TO THE CLAIMS ARE OVERCOME

Claims 57-59 were objected to under 37 C.F.R. §1.75(c) as allegedly being of improper dependent form. The rejection is respectfully traversed.

It is respectfully pointed out that the recitations of claims 57-59 are necessary for there to be proper antecedent basis for claim 60, and that a series of dependent claims similar to these was allowed during the prosecution of parent application U.S. 6,090,625; not, for instance, claims 5 to 8 of the '625 patent. Consequently, the claims have been previously found to be proper. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

V. THE § 112, INDEFINITENESS, REJECTIONS ARE OVERCOME

Claims 47-76 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The rejection is respectfully traversed.

Specifically, claim 47 is rejected due to the use of the term "low," which the Office Action alleges renders the claim indefinite. The Office Action also alleges that the specification does not provide a standard for ascertaining the requisite degree, and that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicants respectfully disagree.

The amendments to the specification herein delete an obviously erroneous statement that the identification of cells as low, medium or high is arbitrary. This error is a mistake that one skilled in the art would readily recognize and the correction for which is, and was at the time of filing, known. *See In re Oda*, 443 F.2d 1200, 170 USPQ 260 (CCPA 1971) (correction of obvious errors in a patent or patent application are permitted and are not new matter).

The terms low, medium and high are known by one of ordinary skill in the art to refer to the antigen density on the surface of a given cell. One of ordinary skill in the art, at the time of filing, would have known the meaning of the term "low" in the context of CD45 low cells, and, would have been able to identify the same population of cells as being CD45 low. To this end, enclosed are a number of abstracts and articles which were published prior to the filing of the present application which regularly use the terminology of "low" and "high" to refer to antigen density (occasionally replaced by the use of "+" or "+++"), see e.g., Sedgwick et al. Isolation and direct characterization of resident microglial cells from the normal and inflamed central nervous system. Proc Natl Acad Sci USA 1991 Aug;88:7438-42; Pilarski et al. Beta 1 integrin (CD29) expression on human postnatal T cell subsets defined by selective CD45 isoform expression. J Immunol 1991 Aug 1;147(3):830-7; and others listed on the PTO 1449. Indeed, it is respectfully submitted that the majority of these abstracts and articles were published before 1996, that is, prior to the priority date of the present application.

Consequently, the use of the terms "low" and "high" is well settled within the art, such that one of ordinary skill in the art would read the statement that the designations were arbitrary and would know that such a statement was an obvious error. The designation of "low", "medium", and "high" is also used as the determination of whether leukocytes expressing CD45

are polymorphonucleur cells, monocytes or lymphocytes, such that one of ordinary skill in the art would immediately recognize the use of the term "CD45 low" and understand exactly what cells were being referenced.

Consequently, the claim terms are clear and definite and no new matter is added.

Thus, reconsideration and withdrawal of the Section 112, second paragraph, rejection is respectfully requested.

VI. THE SECTION 112, NEW MATTER REJECTIONS ARE OVERCOME

Claims 49, 52-62 and 67-72 were rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the Applicant was in possession of the invention at the time of filing, such that the claims recite new matter. The rejection is respectfully traversed.

Specifically, it is alleged that the recitation of "2 to 24 hours" in claim 49 is new matter. Applicants respectfully disagree. The Examiner's attention is respectfully directed to Table 8, for which the Examiner is thanked for pointing out the error in the September 6, 2002 Response which erroneously referred to Table 6.

Table 8 summarizes the results of the experiment described on page 28 of the specification entitled "CD45 and CD14 panel." This experiment involved treating blood samples with monoclonal antibody to the homologous region of the b-chain of HLA-DR and measuring the change in expression of CD45 and CD14. Time 0 of the experiment indicates the time at which the blood samples were treated with the monoclonal antibody. The reaction between the blood sample and the monoclonal antibody was allowed to run for a full 24 hours, during which time analysis of the treated samples occurred at various time points, as shown in Table 8. It is respectfully submitted that by allowing the reaction to occur from 0 to 2 hours, and then from 2 hours to 24 hours (as must occur to enable analysis to be obtained at 24 hours after treatment of the sample), Table 8 does, in fact, support the recitation of "2 to 24 hours."

Consequently, the new matter rejection based on the recitation "2 to 24 hours" should be reconsidered and withdrawn. And thus, reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action further alleges that the recitation in claim 52, "human leukocytes are found in ... bone marrow", constitutes new matter. The rejection is respectfully traversed. The

amendments to the claims herein, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, render the rejection moot. Consequently, reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action still further alleges that the recitation in claim 53 that CD45 low cells are MHC class I+ or class II+ constitutes new matter. The rejection is respectfully traversed. The specification, at page 2, lines 28-29, describes most unidifferentiated and differentiated cells as comprising major Histocompatibility Complex class I antigens and/or class II antigens. The Office Action alleges that this statement does not teach that CD45 low cells are MHC class I+ or class II+ because page 3, lines 11-17 describes various cells as being positive for an MHC class II antigen, without any mention of MCH class I antigens. Applicants respectfully disagree with this reasoning. If a statement says that a cell (or most cells) is MHC class I+ **and/or** class II+, it inherently states that if a cell is class II+, it **cannot** be assumed that it is not also class I+, contrary to the arguments set forth in the Office Action. A listing of the relevant class II antigens, as found on page 3 of the specification, is only that: a listing of the relevant class II antigens. It **cannot** be assumed to be a list of **all** the antigens present on the cell. In fact, it should be noted that the list on page 3 is not exhaustive of all possible antigens on the cells discussed. The listing is merely concerned with a small group of antigens which does not exclude all others, regardless of whether they are class I or class II antigens.

Consequently, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 67-72 are also rejected for allegedly containing new matter because the specification allegedly does not support any of the properties contained therein. The rejection is respectfully traversed.

The Office Action states that the section of the application referred to in the September 6, 2003 response (page 35, lines 22-30) as supporting the recitations of claims 67-72 refers to CD34+ cells, not CD45 low cells, and that extrapolation of the properties of CD34+ cells to CD45 low cells in improper. Applicants respectfully disagree.

One of ordinary skill in the art would recognize that CD34+ cells are always CD45 low. Thus, statements which apply to CD34+ cells also apply to CD45 low cells. For example, CD34+ cells are often sorted by flow cytometry on the basis of their CD45 low expression. Consequently, Applicants respectfully urge that one of ordinary skill in the art at the time of

filing would have readily ascertained that any statements in the specification concerning CD34+ cells also hold true for CD45 low cells. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

VII. THE SECTION 112, POSSESSION REJECTIONS ARE OVERCOME

Claims 47-72 were rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventor had possession of the invention at the time of filing. The rejection is respectfully traversed.

Specifically, the Office Action states that the Applicant was not in possession of the genus of agents which operably engage committed cells, nor of the genus of "biological response modifiers."

Applicants respectfully request that the Examiner review U.S. Patent No. 6,090,625, wherein Applicants were granted claims which encompass the genus of agents which operably engage committed cells, and the genus of "biological response modifiers" which are at issue in the present application; note claims 1 and 18 of the '625 patent. Thus, the genus of agents which operably engage committed cells, and the genus of "biological response modifiers" has already been evaluated by the USPTO and deemed acceptable within the meaning of 35 U.S.C., §112. For this reason alone, the rejection must be withdrawn.

Further, Applicants have provided guidance in the specification as to what agents may be suitably used. There is no requirement to teach each and every agent that may be used. Given the pioneering nature of this invention and the fact that a person skilled in the art may now easily screen for additional agents and biological response modifiers to those used in the Examples in the knowledge that retrodifferentiation of cells to stem cells is actually possible - contrary to earlier teachings - it would seem unreasonable to restrict the scope of the patentee's protection unduly and in the absence of documentary evidence that the claimed scope is unjustified.

Furthermore, not only have Applicants demonstrated at least two agents in the application are suitable for performing the invention and provided guidance as to other suitable agents, but experimental evidence was provided in the Declaration submitted September 6, 2002 which shows that two other agents that are completely unrelated to the agents exemplified in the application,

namely erythropoietin and GM-CSF, also result in the conversion of more committed cells to stem cells (specifically $CD34^-$ cells – which is the same as CD45 low cells) – see Annex A.

It is respectfully submitted that the Examiner should bear in mind that the Applicant has focused on monoclonal antibodies to MHC receptors in the application simply because early studies showed that these agents gave the best results. Consequently, as a laboratory scientist seeking to investigate the process further, the Applicant has used other reagents in subsequent studies. However, it is emphasized that not only have the monoclonal antibodies exemplified in the specification provided the desired results, so have other agents been shown to work, such as those in the previously filed Declaration.

All of the foregoing illustrate that the Applicant was clearly in possession of the genus of agents that operably engage committed cells and the genus of biological response modifiers at the time of filing.

Consequently, reconsideration and withdrawal of the section 112 rejections is respectfully requested.

VIII. THE SECTION 112, ENABLEMENT REJECTIONS ARE OVERCOME

Claims 47-61 and 63-72 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for any agent that operably engages committed cells. The rejection is respectfully traversed.

Claim 63 is also rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for any biological response modifier for use in retrodifferentiating committed cells into CD45 low expressing cells. The rejection is respectfully traversed.

As discussed above, the terms "agent" and "biological response modifier" were previously considered during the prosecution of U.S. Patent No. 6,090,625, during which they were deemed enabled; again, note claims 1 and 18 of the '625 patent. The Examiner is invited to review the prosecution history of U.S. Patent No. 6,090,625, and is urged that on this basis alone, the rejection is improper.

Consequently, reconsideration and withdrawal of the Section 112, enablement rejections is respectfully requested.

IV. THE SECTION 101 REJECTIONS ARE OVERCOME

Claims 47 to 76 are rejected under 35 U.S.C. §101 because the claimed invention is allegedly not supported by either a specific asserted utility or a well established utility. Claims 47 to 76 are also rejected under 35 U.S.C. §112, first paragraph. Specifically, since the claimed invention is allegedly not supported by either a specific asserted utility or a well established utility, one of ordinary skill in the art would not know how to use the claimed invention. The rejections are respectfully traversed.

The Examiner's attention is again directed to Section 5 of the previously filed Declaration, in which the Applicant describes the utility of the invention, and states that one of ordinary skill in the art, at the time of filing, would have known of the potential uses for a population of cells in which the relative number of CD45 low cells is increased. As evidenced in the Declaration, one such use would be in the treatment of leukemia.

The Office Action states that the previously filed Declaration does not adequately demonstrate that as of February 2, 1995, one of ordinary skill in the art would have known that the CD45 low marker is found in stem cells having a hematopoietic or myeloid nature. To this end, the Examiner is respectfully invited to review the accompanying abstracts which demonstrate that prior to February 2, 1995, it was known by those of ordinary skill in the art that the CD45 low marker is found in stem cells having a hematopoietic or myeloid nature; see, e.g., Wickenhauser et al. CD34+ human hemopoietic progenitor cells of the bone marrow differ from those of the peripheral blood: an immunocytochemical and morphometric study. Acta Haematol 1995;93(2-4):83-90.

Additionally, the Office Action states that since the designation of "low" is arbitrary, there is no way to know whether what the art might have recognized as "CD45 low" is the same as what Applicants consider "CD45 low." Applicants disagree. As previously stated, the statement that the designation of "low," "medium," and "high" was arbitrary was an obvious error in the specification which one of ordinary skill in the art at the time of filing would have recognized. Consequently, the rejections based on such erroneous statement are moot.

A population of CD45 low cells were known to be useful in research; for instance CD45 low cells were useful in flow cytometric analyses, e.g., to generate antibodies thereto, for use in flow cytometric analyses. See, e.g., Trischmann et al. Measurement of CD34+ cells in bone marrow by flow cytometry. J Hematother 1993 Fall;2(3):305-13; Abrahamsen et al. Flow

cytometric assessment of peripheral blood contamination and proliferative activity of human bone marrow populations. Cytometry 1995 Jan 1;19(1):77-85; Festin et al. Multicolor flow cytometric analysis of the CD45 antigen provides improved lymphoid cell discrimination in bone marrow and tissue biopsies. J Immunol Methods 1994 Dec 28;177(1-2):215-24; Shah et al. Flow cytometric analysis of human bone marrow. IV. Differential quantitative expression of T-200 common leukocyte antigen during normal hemopoiesis. J Immunol 1988 Mar 15;140(6):1861-7; Dick et al. Flow cytometric identification of a minority population of MHC class II positive cells in the normal rat retina distinct from CD45lowCD11b/c_CD4low parenchymal microglia. Br J Ophthalmol 1995 Sep;79(9):834-40; and, Gane et al. Flow cytometric evaluation of human basophils. Cytometry 1993;14(3):344-8.

Furthermore, the Examiner's attention is respectfully drawn to the accompanying Zhao document (A human peripheral blood monocyte-derived subset acts as pluripotent stem cells. PNAS 2003 100(5):2426-2431), wherein the use of pluripotent stem cells (the equivalent of CD45 low cells) are considered as candidates for transplantation therapy.

Consequently, in light of the remarks and documents cited herein, which demonstrate a real utility as to flow cytometric analyses, treating leukemia and transplantation therapy, reconsideration and withdrawal of the rejections are respectfully requested.

V. THE DOUBLE PATENTING REJECTION IS OVERCOME

NO! NOTHING SUBMITTED

Claims 47-72 were rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-20 of U.S. Patent No. 6,090,625. The rejection is respectfully traversed.

Applicants again note that while Applicants do not agree that there is double patenting between the current application and U.S. Patent No. 6,090,625, in an effort to further prosecution of the present application, Applicants will file a terminal disclaimer upon notification of allowable subject matter. Until such time, it is respectfully requested that the rejection be held in abeyance.

Consequently, reconsideration and withdrawal of the double patenting rejection is respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, prior to any paper issuing other than a Notice of Allowance, another interview is respectfully requested and the Examiner is further respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for the interview.

CONCLUSION

In light of the amendments and remarks made herein, and the enclosures herewith, it is respectfully submitted that the application is now in condition for allowance. Consideration and entry of this paper and of the attachments herewith, early and favorable reconsideration of the application, reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorneys for Applicants

By: _____

Thomas J. Kowalski
Reg. No. 32,147
Amy Leahy
Reg. No. 47,739
Tel (212) 588-0800
Fax (212) 588-0500
Email TKowalski@FLHLaw.com

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE TITLE:

Method of [preparing an undifferentiated cell] increasing the relative number of CD45 low cells in a cell population.

IN THE SPECIFICATION:

Page 34, line 1 to 12:

CD45 AND CD14 PANEL

Blood samples treated with monoclonal antibodies to the - or alpha- chains of the DR antigen or to the -chain plus cyclophosphoamide or class I antigens were also analysed with the CD45 and CD14 panel (Table 18). [The delineation of CD45 low, CD45 high and CD45 medium is arbitrary.] Treatment of blood sample 5/6 (at 2 hours) with monoclonal antibodies to the -chain of the DR antigen or with this monoclonal antibody plus cyclophosphoamide generated $CD45^+$ low cells and increased the relative number of $CD45^+$ medium cells. However, the former treatment increased the relative number of $CD45^+$ high cells and the latter treatment decreased the relative number of $CD45^+$ medium cells and these changes appeared to be time dependent.

IN THE CLAIMS:

52. (Amended) The method according to claim 47, wherein the committed cells are human leukocytes, wherein the human leukocytes are found in peripheral blood, [~~bone marrow~~] thymus spleen or tonsil tissue, and wherein the leukocytes are selected from the group consisting of lymphocytes, monocytes, polymorphonuclear cells, eosinophils and basophills.

54. (Amended) The method according to claim [47]53, wherein the receptor is an MHC class I antigen or an MHC class II antigen.